Topic: The X-Linked Neurodegenerative Disease, Adrenoleukodystrophy (X-ALD)

Related Lectures in Block I: Lipids I: Fatty Acid Beta-Oxidation, and Lipids II: Fatty Acid Synthesis (Maltese)

Learning Objectives:

**1)Describe the major symptoms of X-ALD.**

The most common symptoms are usually behavioral changes such as abnormal withdrawal or aggression, poor memory, and poor school performance. Other symptoms include visual loss, learning disabilities, seizures, poorly articulated speech, difficulty swallowing, deafness, disturbances of gait and coordination, fatigue, intermittent vomiting, increased skin pigmentation, and progressive dementia. In the milder **adult-onset form,** which typically begins between ages 21 and 35, symptoms may include progressive stiffness, weakness or paralysis of the lower limbs, and ataxia. Although adult-onset ALD progresses more slowly than the classic childhood form, it can also result in deterioration of brain function. A **mild form of ALD** is occasionally seen in women who are carriers of the disorder. Symptoms include progressive stiffness, weakness or paralysis of the lower limbs, ataxia, excessive muscle tone, mild peripheral neuropathy, and urinary problems.

**2) Explain why very long chain fatty acids accumulate in patients with X-ALD.**

The VLCSFA "degradative" enzyme is made in the cytoplasm at free ribosomes and then shipped across the peroxisome membrane into the lumen of this organelle. The first enzyme in the degradation path is called very long chain fatty acid (or VLCFA) CoA synthase. This enzyme catalyzes the addition of acetyl-CoA to VLCFA and subsequent degradative reactions are dependent upon this first step.  
Recent research has shown that ALD is not due to a bad VLCFA-CoA synthase but due to a malfunctioning transporter protein that moves the VLCFA-CoA synthase across the peroxisome membrane (Valle and Gartner, 1993). The malfunctioning transporter protein is located in the membrane of the peroxisome and is a member of the ABC transporter family (ABC abbreviates ATP-binding cassette). The ABC transporters move large proteins, amino acids, and ions across membranes and are involved in drug resistance (by pumping drugs out of cells). Malfunction of a related but different ABC transporter is responsible for cystic fibrosis.

**3) Explain why feeding a mixture of unsaturated fatty acids (oleic and erucic acids), “Lorenzo’s Oil” has shown some benefits in treating patients with X-ALD.Limit of dietary VLCFAs still leads to increase in blood VLCFAs.**

This is because VLCFAs are still being synthesized in the ER and cannot be degraded in the peroxisome. Oleic and erucic acids (both unsaturated) act as competitive inhibitors of the enzyme that synthesizes VLCFAs. Erucic acid is an even better competitive inhibiter because it is also a VLCFAs. This is beneficial because the ER will produce unsaturated VLCFAs instead of saturated VLCFAs, (Note: it is saturated VLCFAs that cause ALD because saturated fatty acid is straight (not crooked) and these characteristics would facilitate the ability of VLCSFAs to interact with, insert into or solubilize the hydrophobic myelin sheath. VLCSFAs may act like a "soap" to solubilize or interact with the hydrophobic molecules of the myelin sheath.The exact mechanism of how VLCSFAs cause ALD symptoms is not known. As opposed to the solubilizing effect noted above, the properties of VLCSFAs would allow it to concentrate in the myelin sheath and may cause a local immune reaction that destroys the sheath. Conversely, the properties of VLCSFAs may allow it to concentrate in neural membranes to inhibit membrane function. **Disclaimer**: there is still not cure for ALD, Lorenzo’s Oil might just slow the onset of the symptoms.

**4) Describe the underlying biochemical defect in X-ALD.**

Adrenoleukodystrophy (ALD) is one of a group of genetic disorders called the *leukodystrophies* that cause damage to the myelin sheath, an insulating membrane that surrounds nerve cells in the brain. People with ALD accumulate high levels of saturated, very long chain fatty acids (VLCFA) in the brain and adrenal cortex because they do not produce the enzyme that breaks down these fatty acids in the normal manner. The loss of myelin and the progressive dysfunction of the adrenal gland are the primary characteristics of ALD. ALD has two subtypes. The most common is the **X-linked form (X-ALD),** which involves an abnormal gene located on the X-chromosome. Women have two X-chromosomes and are the carriers of the disease, but since men only have one X-chromosome and lack the protective effect of the extra X-chromosome, they are more severely affected. Onset of X-ALD can occur in childhood or in adulthood. The childhood form is the most severe, with onset between ages 4 and 10.